Leishmaniasis

Dr. Nashwan Mansoor

Leishmaniasis

- **Leishmaniasis is caused by unicellular, flagellate, intracellular protozoa belonging to the genus Leishmania.**

- **Are 21 leishmanial species that cause diverse clinical syndromes.**

- **Three broad groups:-**

- **Visceral leishmaniasis (VL, kala-azar).**
- **Cutaneous leishmaniasis (CL).**
- **Mucosal leishmaniasis (ML).**

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Leishmaniasis

❖ Epidemiology and transmission:-

- Most clinical syndromes are caused by zoonotic transmission of parasites from animals to humans through phlebotomine sand-fly vectors.
- Humans are the only known reservoir (anthroponotic person-to-person transmission) in major VL.
- Leishmaniasis occurs in approximately 100 countries around the world.
- An estimated annual incidence of 0.9–1.3 million new cases (25% VL).

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Leishmaniasis

❖ Epidemiology and transmission:-

➢ The life cycle of Leishmania;-

- Flagellar promastigotes (10–20 µm) are introduced by the feeding female sand-fly.
- The promastigotes are taken up by neutrophils.
- Undergo apoptosis and are then engulfed by macrophages, in which the parasites transform into amastigotes (2–4 µm; Leishman–Donovan body).
- These multiply, causing macrophage lysis and infection of other cells.

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Leishmaniasis

❖ Epidemiology and transmission:-

➢ The life cycle of Leishmania;-

- Sandflies pick up amastigotes when feeding on infected patients or animal reservoirs.
- In the sand-fly, the parasite transforms into a flagellar promastigote, which multiplies by binary fission in the gut of the vector and migrates to the proboscis to infect a new host.
- Sandflies live in hot and humid climates in the cracks and crevices of mud or straw houses and lay eggs in organic matter.
- People living in such conditions are more prone to leishmaniasis.
- Female sandflies bite during the night and preferentially feed on animals; humans are incidental hosts.

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Visceral leishmaniasis (kala-azar)

- VL is caused by the protozoon Leishmania donovani complex.
- India, Sudan, Bangladesh and Brazil account for 90% of cases of VL.
- Other affected regions include the Mediterranean, East Africa, China, Arabia.
- The majority is sand-fly transmission.
- VL reported to follow blood transfusion.

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Visceral leishmaniasis (kala-azar)

- **Disease can present unexpectedly in immunosuppressed patients, for example;-**
  - **After renal transplantation.**
  - **In HIV infection.**
- **The majority of people infected remain asymptomatic.**
- **In visceral disease, the spleen, liver, bone marrow and lymph nodes are primarily involved.**

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Visceral leishmaniasis (kala-azar)

❖ Clinical features :-

- Mainly a disease of small children and infants, except in adults with HIV co-infection.
- The incubation period ranges from weeks to months (occasionally, several years).
- The first sign of infection is high fever, usually accompanied by rigor and chills.
- Fever intensity decreases over time and patients may become afebrile.
- This is followed by a relapse of fever, often of lesser intensity.
- Splenomegaly develop in the first few weeks and becomes massive as the disease progresses.

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Visceral leishmaniasis (kala-azar)

❖ Clinical features :-

- Moderate hepatomegaly occurs later.
- Lymphadenopathy is common in Africa, the Mediterranean and South but is rare in the Indian subcontinent.
- Blackish discoloration of the skin, is a feature of advanced illness but is now rarely seen.
- Pancytopenia is common.
- Moderate to severe Anaemia develops rapidly and can cause cardiac failure.
- Thrombocytopenia, often compounded by hepatic dysfunction, may result in bleeding from the retina, gastrointestinal tract and nose.
- In advanced illness, hypoalbuminemia may manifest as pedal oedema, ascites and anasarca.

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Visceral leishmaniasis (kala-azar)

❖ Clinical features :-

- **The profound immunosuppression and secondary infections are very common in progresses disease. These include:-**
  - **Tuberculosis.**
  - **Pneumonia.**
  - **Gastroenteritis.**
  - **Severe amoebic or bacillary dysentery.**
  - **Boils.**
  - **Cellulitis.**
  - **Chickenpox.**
  - **Shingles.**
  - **Scabies.**

- **Without adequate treatment, most patients with clinical VL die.**

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Visceral leishmaniasis (kala-azar)

❖ Investigations :-

- **Pancytopenia is the dominant feature, with granulocytopenia and monocytosis.**
- **Polyclonal hypergammaglobulinemia, chiefly IgG followed by IgM.**
- **Hypoalbuminemia are seen later.**
- **Demonstration of amastigotes (Leishman–Donovan bodies) in splenic smears:-**
  - **The most efficient means of diagnosis, with 98% sensitivity.**
  - **Carries a risk of serious hemorrhage in inexperienced hands.**

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Visceral leishmaniasis (kala-azar)

❖ Investigations :-

- Bone marrow or lymph node smears, are not as sensitive but are frequently employed.

- Parasites may be demonstrated in buffy coat smears, especially in immunosuppressed patients.

- Sensitivity is improved by:-
  - Culturing the aspirate material.
  - Using PCR for DNA detection.
  - Species identification.

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Visceral leishmaniasis (kala-azar)

❖ Investigations :-

- **Serodiagnosis:-**
  - **In developed countries ELISA or immunofluorescence antibody test.**
  - **In endemic regions, a highly sensitive direct agglutination test.**
  - **These tests remain positive for several months after cure has been achieved, so do not predict response to treatment or relapse.**
  - **The vast majority of people exposed to the parasite do not develop clinical illness but may have positive serological tests thereafter.**
- **Formal gel (aldehyde) or other similar tests, have limited value and should not be employed for the diagnosis of VL.**

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Visceral leishmaniasis (kala-azar)

❖ Differential diagnosis :-

- **Malaria.**
- **Typhoid.**
- **Tuberculosis.**
- **Schistosomiasis.**
- **Many other infectious and neoplastic conditions, some of which may coexist with VL.**

❑ **Fever, splenomegaly, pancytopenia and non-response to antimalarial therapy may provide clues before specific laboratory diagnosis is made.**

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Visceral leishmaniasis (kala-azar)

❖ Management :-

➢ Pentavalent antimonies:-

- ✓ The first drugs to be used for the treatment of leishmaniasis.
- ✓ Remain the mainstay of treatment in most parts of the world.
- ✓ Traditionally, pentavalent antimony is available as sodium stibogluconate (100 mg/mL).
- ✓ The daily dose is 20 mg/ kg body weight, intravenously or intramuscularly, for 28–30 days.
- ✓ Side-effects are common and include arthralgia, myalgia, raised hepatic transaminases, pancreatitis and ECG changes.
- ✓ Severe cardiotoxicity, is not uncommon.

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Visceral leishmaniasis (kala-azar)

❖ Management :-

➢ Amphotericin B :-

❑ Amphotericin B deoxycholate;-

- ✓ **Given once daily or on alternate days at a dose of 0.75–1.00 mg/kg for 15–20 doses.**
- ✓ **The first-line drug in many regions where is a significant level of Sb unresponsiveness.**
- ✓ **Has a cure rate of nearly 100%.**
- ✓ **Infusion-related side-effects, such as high fever with rigor, thrombophlebitis, diarrhoea and vomiting, are extremely common.**
- ✓ **Serious side-effects are observed frequently, including:- renal toxicity, hepatic toxicity, hypokalemia, and thrombocytopenia.**

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Visceral leishmaniasis (kala-azar)

❖ Management :-

➢ Amphotericin B :-

❑ Lipid formulations of amphotericin B ;-

- ✓ **Are less toxic.**
- ✓ **AmBisome is first-line therapy in Europe for VL.**

- ✓ **Dosing recommendations vary according to geographical region.**
- ✓ **A total dose of 10 or 15 mg/kg, administered in a single dose or as multiple doses over several days, respectively.**

- ✓ **High daily doses of the lipid formulations are well tolerated.**
- ✓ **In one study a single dose Of 10 mg/kg of AmBisome cured 96% of Indian patients.**

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Visceral leishmaniasis (kala-azar)

❖ Management :-

➢ Other drugs :-

- ❑ Miltefosine.
- ❑ Paromomycin.
- ❑ Pentamidine isethionate.

Visceral leishmaniasis (kala-azar)

❖ Management :-

- **Multidrug therapy of VL is likely to be used increasingly to prevent emergence of drug resistance.**

- **Response to treatment;-**

  - **A good response results in fever resolution, improved well-being, reduction in splenomegaly, weight gain and recovery of blood counts.**

  - **Patients should be followed regularly for 6–12 months, as some may experience relapse irrespective of the treatment regimen.**

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Post-kala-azar dermal leishmaniasis

- After treatment and apparent recovery from VL in India and Sudan, some patients develop dermatological manifestations due to local parasitic infection.

❖ Clinical features:-

- Dermatological changes occur in a small minority of patients 6 months to at least 3 years after the initial infection.

- Are seen as macules, papules, nodules (most frequently) and plaques, which have a predilection for the face, especially the area around the chin.

- The face often appears erythematous.

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Post-kala-azar dermal leishmaniasis

❖ Clinical features:-

- **Hypopigmented macules can occur over all parts of the body and are highly variable in extent.**
- **No systemic symptoms and little spontaneous healing occurs.**
- **In addition to the dermatological features, a measles-like micropapular rash may be seen all over the body.**
- **Spontaneous healing occurs in about three-quarters of cases within 1 year.**

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Post-kala-azar dermal leishmaniasis

❖ Investigations and management :-

- The diagnosis is clinical, supported by demonstration of scanty parasites in lesions by slit-skin smear and culture.

- Immunofluorescence and immunohistochemistry may demonstrate the parasite in skin tissues.

- In the majority of patients, serological tests (direct agglutination test or k39 strip tests) are positive.

- Treatment of PKDL is difficult.

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Post-kala-azar dermal leishmaniasis

❖ Investigations and management :-

- **The drugs used in treatment are:-**
  - **Stibogluconate.**
  - **Amphotericin B infusions.**
  - **Miltefosine.**
- **In the absence of a physical handicap, most patients are reluctant to complete the treatment.**
- **PKDL patients are a human reservoir, and focal outbreaks have been linked to patients with PKDL in areas previously free of VL.**

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Visceral leishmaniasis (kala-azar)

❖ Prevention and control :-

- Sand-fly control through insecticide spray is very important.
- Mosquito nets or curtains treated with insecticides will keep out the tiny sandflies.
- In endemic areas with zoonotic transmission, infected or stray dogs should be destroyed.
- In areas with anthroponotic transmission, early diagnosis and treatment of human infections, to reduce the reservoir and control epidemics of VL, is extremely important.
- Serology is useful in diagnosis of suspected cases in the field.
- No vaccine is currently available.

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Cutaneous and mucosal leishmaniasis

❖ Cutaneous leishmaniasis :-

- CL (oriental sore) occurs in both the Old World (Asia, Africa and Europe) and the New World (the Americas).
- In the Old World, CL is mild.
- The causative organisms for Old World zoonotic CL are L. major, L. tropica and L. aethiopica.
- Anthroponotic CL is caused by L. tropica, and is confined to urban or suburban areas of the Old World.
- In recent years, there has been an increase in the incidence of zoonotic CL in both the Old and the New Worlds due to urbanization and deforestation.
- New World CL is a more significant disease, which may disfigure the nose, ears and mouth.
- CL is commonly imported and should be considered in the differential diagnosis of an ulcerating skin lesion, especially in travelers who have visited endemic areas.

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Cutaneous and mucosal leishmaniasis

❖ Cutaneous leishmaniasis :-

❑ Pathogenesis :-

- **Inoculated parasites are taken up by dermal macrophages, in which they multiply and form a focus for lymphocytes, epithelioid cells and plasma cells.**

- **Self-healing may occur with necrosis of infected macrophages, or the lesion may become chronic with ulceration of the overlying epidermis, depending on the a etiological pathogen.**

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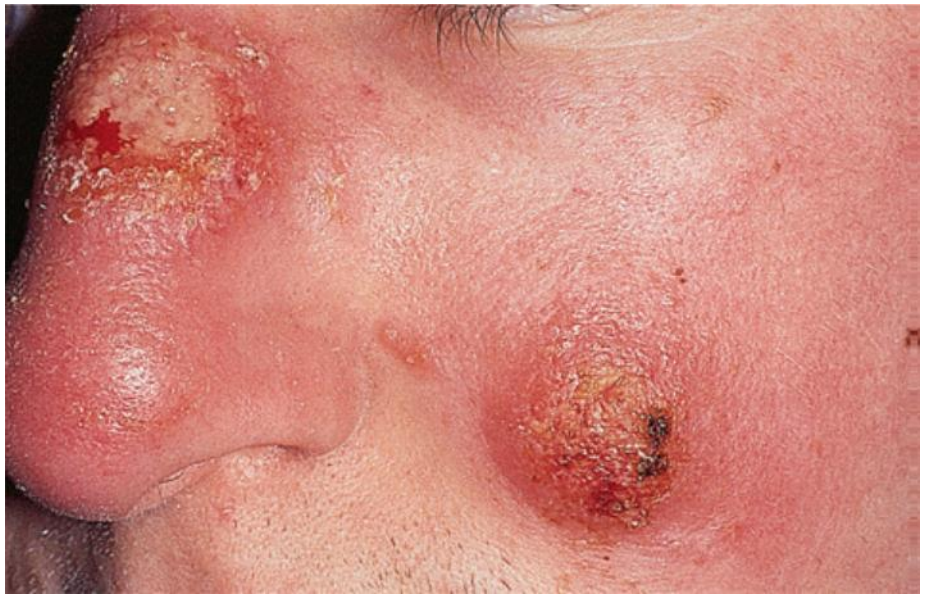
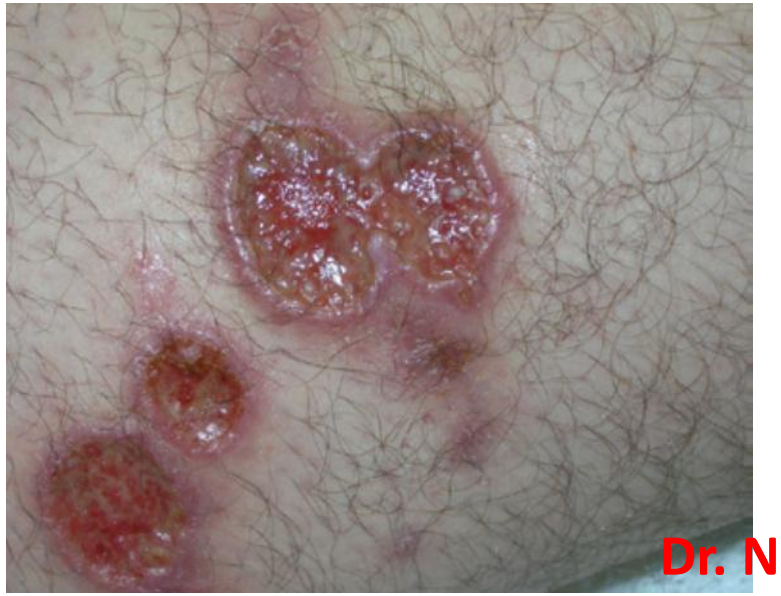
Cutaneous and mucosal leishmaniasis

❖ Cutaneous leishmaniasis :-

❑ Clinical features :-

- **The incubation period is typically 2–3 months (range 2 weeks to 5 years).**
- **In all types of CL a papule develops at the site of the vector bite.**
- **The small, red papules may be single or multiple and increase gradually in size, reaching 2–10 cm in diameter.**
- **A crust forms, overlying an ulcer with a granular base and with raised borders**





Cutaneous and mucosal leishmaniasis

❖ Cutaneous leishmaniasis :-

❑ Clinical features :-

- Ulcers develop a few weeks or months after the bite.
- Can be satellite lesions, especially in L. major and occasionally in L. tropica infections.
- Regional lymphadenopathy, pain, pruritus and secondary bacterial infections may occur.
- lesions on the pinna of the ear are common and are chronic and destructive.
- In some patients development of diffuse CL; this is characterized by spread of the infection from the initial ulcer, usually on the face, to involve the whole body in the form of non-ulcerative nodules.
- Occasionally, in *L. tropica* infections, sores that have apparently healed relapse persistently (recidivans or lupoid leishmaniasis).

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Cutaneous and mucosal leishmaniasis

❖ Mucosal leishmaniasis :-

- **Is responsible for deep sores and ML.**

- **In Leishmania complex infections;-**

✓ **Cutaneous lesions may be followed by mucosal spread of the disease simultaneously or even years later.**

✓ **Young men with chronic lesions are particularly at risk.**

✓ **2–40% of infected persons develop ‘espundia’, metastatic lesions in the mucosa of the nose or mouth.**

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Cutaneous and mucosal leishmaniasis

❖ Mucosal leishmaniasis :-

- **Characterized by thickening and erythema of the nasal mucosa, typically starting at the junction of the nose and upper lip. Later, ulceration develops.**

- **The lips, soft palate, faces and larynx may also be invaded and destroyed, leading to considerable suffering and deformity.**

- **There is no spontaneous healing, and death may result from severe respiratory tract infections due to massive destruction of the pharynx.**

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Cutaneous and mucosal leishmaniasis

❖ Investigations in CL and ML :-

- **CL is often diagnosed on the basis of the lesions' clinical characteristics.**
- **Parasitological confirmation is important, however, because clinical manifestations may be mimicked by other infections.**
- **Amastigotes can be demonstrated on a slit-skin smear with Giemsa staining; alternatively, they can be cultured from the sores early during the infection.**
- **Parasites seem to be particularly difficult to isolate from sores caused by L. brasiliensis, responsible for the vast majority of cases in Brazil.**
- **Touch preparations from biopsies and histopathology usually have a low sensitivity.**

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Cutaneous and mucosal leishmaniasis

❖ Investigations in CL and ML :-

- Culture of fine needle aspiration material has been reported to be the most sensitive method.
- ML is more difficult to diagnose parasitological.
- The leishmania skin test measures delayed-type hypersensitivity to killed *Leishmania* organisms.
- A positive test is defined as induration of more than 5 mm, 48 hours after intradermal injection.
- The test is positive, except in diffuse CL and during active VL.
- PCR is used increasingly for diagnosis and speciation, which is useful in selecting therapy.

Cutaneous and mucosal leishmaniasis

❖ Management of CL and ML :-

- **Small lesions may self-heal or are treated by freezing with liquid nitrogen or curettage.**
- **There is no ideal antimicrobial therapy.**
- **Treatment should be individualized on the basis of the causative organism, severity of the lesions, availability of drugs, tolerance of the patient for toxicity, and local resistance patterns.**
- **In CL, topical application of paromomycin 15% plus methylbenzethonium chloride 12% is beneficial.**

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Cutaneous and mucosal leishmaniasis

❖ Management of CL and ML :-

- **Intralesional antimony seems to be rapidly effective in suitable cases; it is well tolerated and economic, and is safe in patients with cardiac, liver or renal diseases.**
- **In ML, and in CL when the lesions are multiple or in a disfiguring site, it is better to treat with parenteral Sb or with conventional or liposomal amphotericin B.**
- **Sb is also indicated to prevent the development of mucosal disease.**
- **Refractory CL or ML should be treated with an amphotericin B preparation.**

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Cutaneous and mucosal leishmaniasis

❖ Management of CL and ML :-

- Two to four doses of pentamidine, administered on alternate days.
- In ML, 8 injections of pentamidine on alternate days cure the majority of patients.
- Ketoconazole has shown some potential against L. mexicana infection.
- Fluconazole (200 mg daily for 6 weeks) reduced healing times and cured 79% of patients with CL caused by L. major.
- Itraconazole (200 mg daily for 6 weeks) produced good results in CL.

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Cutaneous and mucosal leishmaniasis

❖ Prevention of CL and ML :-

- **Personal protection against sand-fly bites is important.**

- **No effective vaccine is yet available.**